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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/371,347	08/10/1999	ROY A. GRAVEL	50004/003003	9130

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EXAMINER	
RAMIREZ, DELIA M	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 11/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/371,347	GRAVEL ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 21 October 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *21 October 2004*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☒ The proposed amendment(s) will not be entered because:

(a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: *see attached*.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attached*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *none*.

Claim(s) objected to: *3 and 38*.

Claim(s) rejected: *1,2,4,5,36,37,41-43,45-47 and 52-55*.

Claim(s) withdrawn from consideration: *47 and 48*.

8.☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

ADVISORY ACTION

1. Claims 1-5, 36-38, 41-43, 45-49, 52-55 are pending.

2. The request for canceling claims 1-5, 36-38, 41-43, 45-47, 52-55, adding new claims 56-75, submission of a reference by Moroni et al, and arguments filed on 10/21/2004 under 37 CFR 1.116 in reply to the Final Action mailed on 5/19/2004 are acknowledged. The proposed amendments to the claims have been considered. While amendments to the claims seem to overcome the 35 USC 112, second paragraph rejections, and some of the grounds of rejections previously applied in regard to 35 USC 112, first paragraph, the proposed amendments do not overcome some of the 35 USC 112, first paragraph ground(s) of rejection previously applied and raise new issues which would require further consideration as discussed below. Thus, the proposed amendments to the claims will not be entered.

3. New claim 68 would be rejected under 35 USC 112, second paragraph to due to the recitation of "the antisense nucleic acid molecule of claim X, wherein said ... comprises a naturally-occurring mutation or polymorphism present in a mammalian methionine synthase reductase gene". It is noted that the antisense nucleic acids of claims 63 or 65 can have any size and do not have to be related to a mammalian methionine synthase reductase. Thus, the presence of a polymorphism in a nucleic acid which is not related to a mammalian methionine synthase reductase gene is indefinite. See extensive discussion of this issue in page 3, section 6 of the Final Action mailed on 5/19/2004.

4. New claims 74-75 would be rejected under 35 USC 112, second paragraph to due to the recitation of "the nucleic acid molecule of claim 72 or 73" as it is unclear which nucleic acid is being referred to in regard to claim 73. It is noted that claim 73 refers to two nucleic acids, i.e. the antisense nucleic acid and the nucleic acid isolated in step (a). It is suggested that the specific nucleic acid being referred to in claims 74-75 be clearly stated in the claims. For claim interpretation, it will be assumed that claim 74 is directed to the nucleic acid of claim 72 wherein said mammalian methionine synthase reductase polypeptide comprises a consensus binding site for one or more cofactors....wherein said binding site

comprises any one of SEQ ID NO: 25, 52-61. Claim 75 will be interpreted as being directed to the nucleic acid of claim 72, wherein the nucleotide sequence of said nucleic acids comprises a naturally-occurring mutation or polymorphism present in a mammalian methionine synthase reductase gene.

5. New claims 65-68 and 73 would be rejected under 35 USC 112, first paragraph as lacking written description. Claims 65-68 and 73 are directed to a genus of nucleic acids of any size which share at best 18 contiguous nucleotides of polynucleotides which are between 2094-2097 nucleotides long (SEQ ID NO: 1, 41, 43, 45, and 47), and decrease the expression of any methionine synthase reductase polypeptide. No information has been provided in regard to the structural elements required in the genus of antisense nucleic acids recited which would allow for the reduction of expression of any gene encoding a methionine synthase reductase. Also, while a sufficient written description of a genus of polynucleotides may be achieved by a recitation of a representative number of polynucleotides defined by nucleotide sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus, in the instant case, the recited structural features do not constitute a substantial portion of the genus as the remainder of any nucleic acid comprising said structural elements is completely undefined and the specification does not define the remaining structural features for members of the genus to be selected. Thus, many structurally unrelated polynucleotides are encompassed by these claims.

6. New claims 63-68, 72-75 would be rejected under 35 USC 112, first paragraph, scope of enablement. Claims 63-64 are directed to a genus of nucleic acids of any size which hybridize under specific hybridization conditions to the polynucleotides of SEQ ID NO: 1, 41, 43, 45 or 47 and decrease the expression of any methionine synthase reductase polypeptide. The hybridization conditions are such that it is expected the genus of nucleic acids claimed to have low sequence identity to the polynucleotides of SEQ ID NO: 1, 41, 43, 45, and 47. Claims 65-68 and 73 are directed to a genus of nucleic acids which share at best 18 contiguous nucleotides of polynucleotides which are between 2094-2097

nucleotides long (SEQ ID NO: 1, 41, 43, 45, and 47), and decrease the expression of any methionine synthase reductase polypeptide. The specification provides no clue as to the structural elements, in addition to the structural elements recited in the claims, required in those antisense nucleic acids such that they can reduce expression of any methionine synthase reductase polypeptide. The reference by Moroni et al. has been fully considered. While the Examiner is not disputing that a nucleic acid molecule can be made by an skilled artisan, making one having the structural characteristics recited and the functional characteristics required, i.e. capable of reducing expression of any methionine synthase reductase gene, would require undue experimentation in the absence of some knowledge or guidance as to which additional elements in addition to those recited in the claims are required such that expression reduction is achieved. It is noted that the antisense nucleic acids encompassed by the claims can be of any size and the structural features required may represent only a small fraction of such antisense nucleic acid. The art teaches many examples of even how fragments which are completely complementary to contiguous regions of a gene fail to reduce expression of a target mRNA. While fragments of the complete complement of the polynucleotides of SEQ ID NO: 1, 41, 43, 45, 47 are enabled by the teachings of the specification, the entire genus of antisense nucleic acids claimed is not enabled. Claims 72, 74 and 75 (as interpreted above) are directed to a genus of polynucleotides encoding a mammalian methionine synthase reductase wherein said polynucleotides are at least 90% sequence identical to SEQ ID NO: 1. The amount of variability encompassed by the claims is equivalent to 70 amino acids (70 = 210/3) since 10% of a polynucleotide of 2097 is approximately 210 nucleotides. The specification provides no teaching as to which nucleotides can be modified as required and still encode polypeptides having the desired function. Thus, the full scope of the claimed invention is not enabled by the teachings of the specification.

7. The rejections previously applied are, therefore, maintained for the reasons of record in view of the non-entry of the proposed amendments.

8. For purposes of Appeal, the status of the claims is as follows:

Claim(s) allowed: NONE

Claims(s) objected to: 3 and 38

Claim(s) rejected: 1-2, 4-5, 36-37, 41-43, 45-47, 52-55

Claim(s) withdrawn from consideration: 48-49

9. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

10. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
November 10, 2004

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600